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FAMILY PLANNING (A BURKE, SECTION EDITOR)

Injectable Contraception: Current Practices and Future Trends

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Abstract Injectable contraception includes progestin-only and combined estrogen and progestin agents that provide safe and highly effective birth control for one to three months. Injectable agents are widely available and play an important role in family planning programs worldwide. Depot medroxyprogesterone acetate, available for intramuscular injection and subcutaneous injection, is the best known and most broadly distributed injectable contraceptive agent, and is an ideal agent for women who have contraindications to estrogen use. Despite their effectiveness, progestin-only injectables are associated with high rates of discontinuation due to bothersome side effects including abnormal bleeding, health controversies including decreased bone mineral density, and increased risk of human immunodeficiency virus acquisition. Injectables do offer non-contraceptive benefits including symptom control related to endometriosis and fibroids, and decreased risk of endometrial cancer. Research is ongoing to determine new injectable hormone formulations that provide longer-acting contraceptive protection and fewer side effects.

Keywords Depot medroxyprogesterone acetate · DMPA · Injectable contraception · Progestin-only injectable · NET-EN · Mesigyna · Cyclofem · Family planning

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Introduction

Injectable contraceptives have been used globally since the 1980s. Injectable contraceptives offer safe and effective birth control for women who desire a method that is discreet, convenient, reversible, and non-coital-dependent. Depot medroxyprogesterone acetate (DMPA) is the most frequently used injectable, distributed in 179 countries, and is the only injectable agent available in the United States [1]. Other injectable alternatives include a bimonthly progestin-only injectable (POI) containing norethisterone enantate (NET-EN) and several monthly combination injectable contraceptives (CICs) including medroxyprogesterone acetate and estradiol cypionate (MPA/E_2C).

Contraceptive Method and Efficacy

Injectable contraceptive agents primarily inhibit ovulation by gonadotropin suppression via negative feedback of progestin on the hypothalamus [1]. After injection, the agent quickly reaches a peak serum concentration that plateaus and then eventually falls to a minimum effective concentration at which time a repeat injection is indicated. With "perfect use" of the 150 mg intramuscular formulation of DMPA (DMPA-IM), the expected annual pregnancy rate is 0.2 %, versus 6 % with actual or typical use [2]. DMPA is also available in a different formulation for subcutaneous injection of 104 mg (DMPA-SC) with lower peak serum concentration, equal efficacy up to 13-15 weeks, and a similar side effect profile apart from higher risk of injection-site reactions [3]. NET-EN has been found to be as effective as DMPA [4]. CICs are also highly effective with an annual expected pregnancy rate between 0-0.4 % with perfect use [5].

US and International Use

In 2010, 3.8 % of US women using contraception reported current use of DMPA while 23 % reported ever using this contraceptive method [6]. Demographic data demonstrate higher DMPA utilization among adolescents and non-Caucasians [7]. The likelihood of one-year discontinuation among DMPA users due to dissatisfaction is 44.0 %; in comparison, the rate is 32.7 % for oral contraceptive pill users [8].

The 2013 worldwide prevalence of injectable contraceptive use among partnered women was 4.1 % [9]. When narrowed to the least developed countries, the prevalence is 10.5 % [9]. Injectable contraceptives have become exponentially more popular in eastern Africa and South Africa since the 1990s, with 40-55 % of all modern contraceptive users choosing this method [10]. NET-EN is available in 91 countries and five different CIC formulations are available in over 30 countries including many central and South American countries. NET-EN and CICs are popular options internationally; however, DMPA remains the most frequently used injectable agent worldwide due to low cost and wide distribution by foreign aid programs [11].

Administration

Safety

The majority of women requesting injectable contraception will be appropriate candidates to safely receive these medications. For women with preexisting medical conditions, the US Medical Eligibility Criteria for Contraceptive Use (MEC), an adaptation of the corresponding WHO guidelines [12••], provides evidence-based guidance from the Centers for Disease Control and Prevention (CDC) in the US setting [13••]. Providers should be aware of the specific conditions for which POI use should be closely evaluated (Table 1).

In the international setting, WHO MEC provides recommendations for CIC use that align with those for other combined hormonal contraceptives (CHCs). These recommendations may evolve since CICs contain estradiol, which is less potent than synthetic oral estrogen preparations, and data suggest that use of these formulations may not result in a hypercoagulable state [12••, 14].

Provision of Initial Injection

Injectable contraception can be initiated any time in a woman's cycle if the prescriber is reasonably certain that the woman is not pregnant; otherwise a back-up method must be used for seven days [15••, 16]. If a woman is at risk for unintended pregnancy at the time of presentation, appropriate emergency contraception should be offered. An algorithm (Fig. 1) can be used to navigate timing of initial injections with respect to concern for unintended pregnancy. DMPA exposure in early pregnancy has not been shown to cause birth defects [1], but an older study from Thailand demonstrated that it may be associated with low birth weight infants [17]. A newer population-based study from Norway shows an increased risk of preterm delivery with use of DMPA four months to one year prior to conception (aOR 1.83, CI 1.06-3.18); however, there was insufficient data to evaluate exposure of DMPA within four months of conception or in early pregnancy [18]. There is no exam or test required prior to administration of POI to a healthy, asymptomatic woman who denies medical comorbidities; however, baseline weight and body mass index (BMI) may be helpful [15••]. Blood pressure should be measured if possible prior to CIC administration, but should not restrict access to a desired injection if not obtainable [16].

Provision of Repeat Injections

Ongoing DMPA injections should be administered 13 weeks from the prior injection. According to the US Selected Practice Recommendations (SPR), early injection may be given when necessary. Late injection may be administered up to 15 weeks. After this time period, pregnancy may be of concern and a one week back-up method is compulsory [15••]. In contrast, WHO guidance permits routine reinjection up to 17 weeks from the prior injection [19]. This alternative recommendation derives from a study of 2,290 international DMPA users where no difference was found in pregnancy rates at 13, 15, or 17 weeks from prior injection [20]. The US SPR has not adopted this extended grace period since a large proportion of study participants (37.3 %) were breastfeeding; therefore, the study's findings may not be generalizable [15••]. Alternatively, NET-EN is prescribed every two months, and can be administered up to two weeks early or two weeks late [16].

Repeat CIC injections should be administered every four weeks; early injection can be given up to seven days in advance, and a late injection up to seven days beyond the scheduled injection date [16].

New trends in Use and Administration

DMPA-SC is currently being investigated for home self-administration as a possible means of improving contraception continuation rates. Many other frequently used subcutaneous medications, including insulin, are successfully administrated at home, indicating the same could be true for contraceptive agents. Evidence suggests excellent feasibility and high satisfaction with

Table 1 US and WHO MEC: Category 3 and 4 conditions for progesterone-only injectable contraceptive use

CONDITION	DMPA/NET-EN CATEGORY	EVIDENCE/COMMENTS
Multiple risk factors for CV disease or: • Uncontrolled hypertension • Vascular disease • Ischemic heart disease • Stroke • DM 20+ yrs. or with end organ damage	3	Progestins may be associated with increased cardiovascular events in women with risks for or with current cardiovascular disease [77]. Decreasing HDL and increasing LDL has been observed in POI users [78]. Any effects may persist even after discontinuation.
Acute DVT/PE not on anticoagulant therapy	2 (US MEC) 3 (WHO MEC)	Limited evidence suggests non-contraceptive progestin therapy may be associated with VTE [79].
Migraine with aura	2 (initiation) 3 (continuation)*	Aura is a focal neurologic symptom associated with 2-fold increased risk of stroke in COC users [31].
SLE with: • Positive antiphospholipid antibodies • Severe thrombocytopenia	 3 3 (initiation) 2 (continuation)	Antiphospholipid antibodies are associated with increased thrombosis risk [80]. Thrombocytopenia increases bleeding risk; bleeding patterns are unpredictable after POI initiation.
Severe liver disease: • Decompensated cirrhosis • Hepatocellular adenoma • Malignant hepatoma	3	COCs are associated with development of benign hepatocellular adenoma [81]; it is unknown if other hormonal contraceptives have the same effect.
Unevaluated vaginal bleeding suspicious for a serious condition	3	POIs are associated with abnormal bleeding and may mask underlying symptoms of other pathology.
Breast cancer: • Current • Past, no disease for>5 years	 4 3	Breast cancer is often hormonally responsive.
Rheumatoid arthritis on long-term corticosteroids or with history of or other risk factors for non-traumatic fracture	3	DMPA leads to BMD loss; long term corticosteroid use increases risk of non-traumatic fractures [52].
Breastfeeding: •<1 month postpartum •<6 weeks postpartum	 2 (US MEC) 3 (WHO MEC)	No high quality evidence is available to determine long-term effects of POIs on breastfeeding outcomes or safety of exposure in infants [17].

Category 1: A condition for which there is no restriction for use of the contraceptive method

Category 2: A condition where the advantages of using the method generally outweigh the theoretical or proven risks

Category 3: A condition for which theoretical or proven risks usually outweigh the advantages of using the method

Category 4: A condition that represents an unacceptable health risk if the contraceptive method is used

* Initiation refers to starting a new method in a patient with a pre-existing condition; continuation refers to continuing a method in a patient who develops a new condition after starting the method

Adapted from the United States and World Health Organization Medical Eligibility Criteria for Contraceptive Use, 2010

WHO World Health Organization, *MEC* Medical eligibility criteria, *DMPA* Depo medroxyprogesterone acetate, *NET-EN* Norethisterone enanthate, *CV* Cardiovascular, *DM* Diabetes mellitus, *HDL* High density lipoprotein, *LDL* Low density lipoprotein, *POI* Progesterone-only injectable, *DVT* Deep vein thrombosis, *PE* Pulmonary embolism, *VTE* Venous thromboembolism, *SLE* Systemic lupus erythematosus, *COC* Combined oral contraceptive, *DMPA* Depo medroxyprogesterone acetate, *BMD* Bone mineral density

home self-injection of DMPA-SC, though self-injection is not currently specifically endorsed in the drug label [21•].

To improve global access to reproductive health services, the World Health Organization (WHO) and other organizations recommend that appropriately trained community-based health workers (CHWs) screen, counsel, and administer POIs [22]. An international review of DMPA injection programs delivered by CHWs cites that such programs are associated with appropriate client screening, excellent provider and client satisfaction, increased uptake of family planning services, and similar or modest improvement in long-term injection adherence [23•]. A multi-organization project is

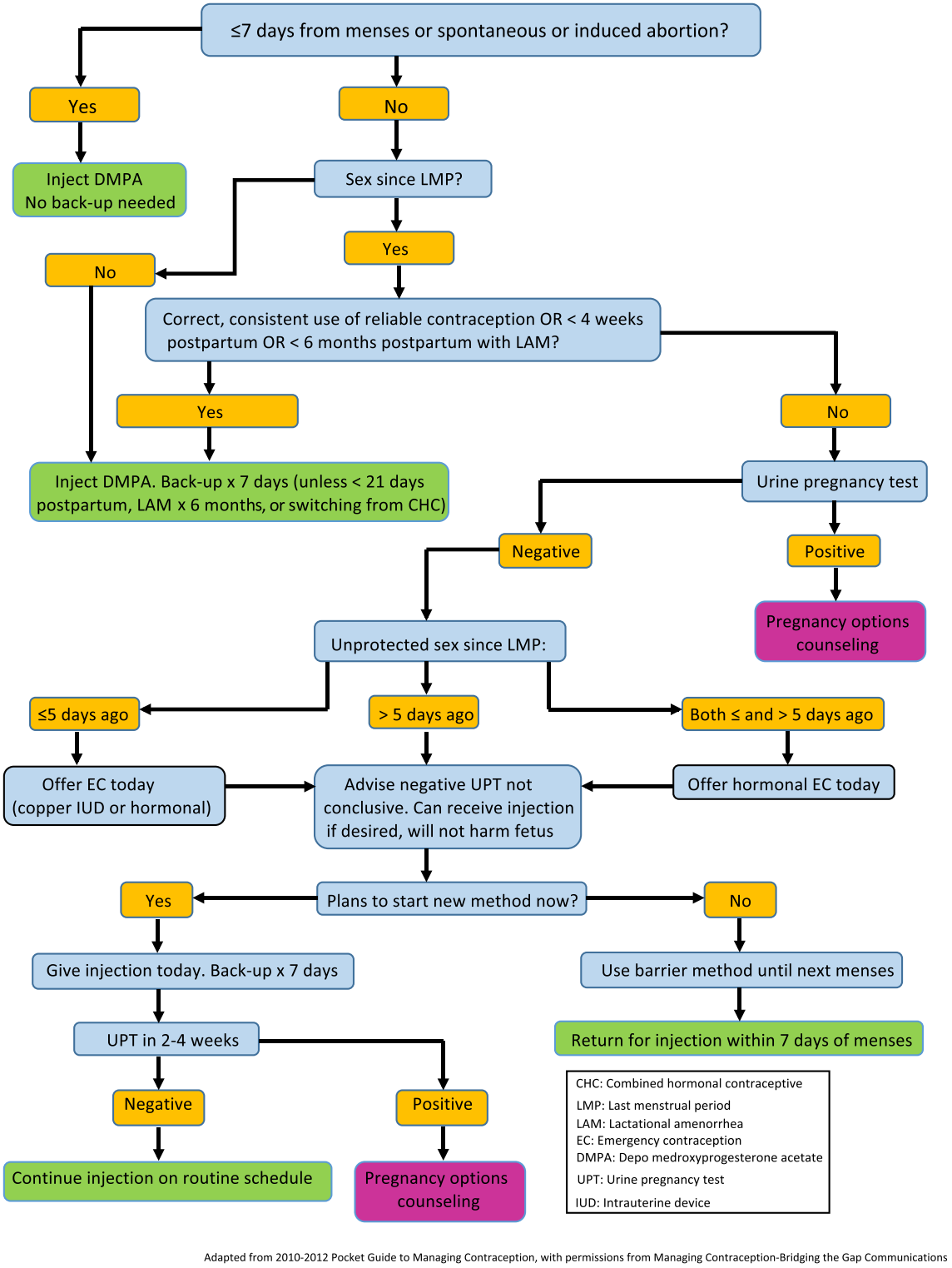

Fig. 1 Algorithm used to navigate timing of initial injections with respect to concern for unintended pregnancy

ongoing to distribute DMPA-SC as Sayana® Press (Pfizer, Inc., New York, NY) in the prefilled, auto-disposable Uniject™ system (Becton Dickison and Company, Franklin Lakes, NJ). Uniject™ is a single-use blister pack of medication that has been successful for many medications including oxytocin for postpartum hemorrhage; it has the potential to further extend the use of DMPA beyond traditional clinical settings [24]. In this instrument, DMPA-SC is portable, easy to inject requiring no additional supplies, and kept stable at room temperature for up to three years [25]. Preliminary data

shows that internationally both providers [26] and patients [27] are satisfied with Sayana® Press and prefer it to DMPA-IM.

Non-contraceptive Use

Endometriosis and Uterine Fibroids

Progestin preparations, including DMPA-IM and DMPA-SC, have been shown to be effective for pelvic pain attributed to endometriosis [28], and are similarly effective as alternative therapies including combined oral contraceptives (COCs) and leuprolide acetate when used for at least six months [29, 30]. DMPA use for at least six months has also been demonstrated to decrease menorrhagia and reduce uterine size among women with leiomyoma [31], although no data from a randomized controlled trial are available [32]. Prospective data from an African-American cohort demonstrated a 40 % reduction in risk of development of clinically significant uterine leiomyoma among current DMPA users [33].

Hematologic Disorders

DMPA is safe for women with sickle cell disease. Evidence suggests that it may decrease the incidence of pain crises when used for at least three consecutive injections; however, data is limited to one small randomized controlled trial and a few small observational studies [34]. DMPA has not been shown to be effective in prevention of menorrhagia among women undergoing myelosuppressive treatment with resultant thrombocytopenia [35]. However, in a small international cohort of chronically anticoagulated women with heart valves who presented with a hemorrhagic corpus luteum cyst, initiation of DMPA treatment was well tolerated for up to three years of follow-up with no recurrent hemorrhagic cysts and no major bleeding side effects [36]. DMPA has been shown to increase hemoglobin levels among women with anemia secondary to fibroid-related heavy menstrual bleeding [31].

Neurologic Disorders

Increase in frequency of headaches has been reported in POI users; however, women who suffer from "menstrual migraine" or estrogen-withdrawal migraine may benefit from use of DMPA or other methods that suppress ovarian activity [37]. CHCs are not recommended in women with migraine over the age of 35 or migraine with aura at any age due to increased risk of ischemic stroke, but the benefits of DMPA initiation are considered to generally outweigh risks in women with these conditions [13••] (see Table 1).

For women with epilepsy, seizure activity may decrease during the luteal phase when progesterone dominates. A very small nonrandomized study using an unspecified intravenous progestin formulation for treatment of hospitalized women with epilepsy found a trend towards decreased seizure frequency in four of seven women in a cohort [38]. A current review on contraceptive options for women with epilepsy in the neurology literature does not cite this research nor purport seizure reduction as a possible benefit of DMPA [39]. CHCs, progestin-only pills, NET-EN, and etonogestrel implants are likely to have had reduced effectiveness when used in conjunction with commonly prescribed anti-seizure medications; conversely, no drug interactions have been found with the use of DMPA [12••].

Gynecologic Cancer Prevention

Ever-use of DMPA is associated with a 60-80 % reduction in the diagnosis of adenocarcinoma of the endometrium [40]. Data are mixed regarding whether DMPA use provides protection from development of epithelial ovarian cancer. A landmark WHO trial found no correlation between DMPA use and risk of epithelial ovarian cancer [41], but a more recent study reported significant risk reduction with DMPA use greater than for three years [42].

Evidence is inconclusive regarding the risk of human papilloma virus (HPV) acquisition and cervical intraepithelial neoplasia (CIN) with DMPA use, but such use demonstrates no increased risk of cervical cancer diagnosis. One US case-control study noted a slightly increased risk of detection of oncogenic human papilloma virus among current DMPA users with greater than one year of use, in comparison to never-users or COC-users, but no increase in cytological abnormalities or cervical intraepithelial neoplasia [43]. Conversely, another US randomized controlled trial following women with pre-existing low-grade cervical cytology abnormalities over two years demonstrated no increased risk of detecting oncogenic HPV in DMPA users, but an increased risk of developing CIN 3 [44]. An international case-control trial with a high percentage of POI users comparing women with invasive cervical cancer to HPV-positive controls found no increased risk of cervical cancer diagnosis with ever-use or never-use of POIs [45].

DMPA use or past use does not increase the risk of breast cancer; however, some data suggest that recent or current DMPA use may influence pre-existing latent breast cancer [46]. In a recent retrospective case-control study of US women aged 22-44 years, DMPA use of at least one year within the past five years was associated with a two-fold increase in diagnosis of invasive breast cancer. However, there was no increased risk associated with recent DMPA use for less than one year or for any duration of use greater than five years prior [47]. In another retrospective case-control study of US women

aged 35-64 years, no risk of breast cancer diagnosis was found with current or prior DMPA use, regardless of age at time of first use, or length of use, or recency of use [48]. If DMPA does influence breast cancer, absolute risk remains low, given the rarity of breast cancer diagnoses in younger women.

Side Effects and Considerations

Bleeding Profile

POIs are associated with a high prevalence of bleeding irregularities. With DMPA, the number of bleeding and spotting days declines with use, from 20.6 days in the first 90-day interval to 9.6 days in the fourth [49]. The likelihood of amenorrhea increases to 12 %, 25 %, 37 %, and 46 % with consecutive 90-day intervals of use [49]. These patterns are consistent for DMPA-IM and DMPA-SC [50]. In the United States, 33.7 % of DMPA-IM users discontinue the method specifically due to changes in menses [51]. Counseling women regarding expected side effects including bleeding prior to use has been shown to improve contraceptive continuation [52]. While prophylactic estrogen supplementation reduces abnormal bleeding when initiated concurrently with DMPA, discontinuation rates of DMPA due to irregular bleeding do not differ based on small trials [53•, 54]. A single small trial compared 50 mg of oral mifepristone, a progestin-receptor antagonist, to placebo administered every 14 days for up to 28 weeks and found that abnormal bleeding among new DMPA users was significantly decreased. Long- term follow-up was not available [55]. More studies are needed to determine the safety and efficacy of these regimens [53•].

For patients requesting treatment for acutely abnormal bleeding persisting beyond seven days, oral ethinyl estradiol 50 mcg daily for 14 days is effective at stopping bleeding when compared to placebo. However, overall long-term DMPA continuation rates did not change [56]. Limited evidence from small studies suggests that short-term NSAIDs (valdecoxib at 40 mg per day for 5 days [57], mefenamic acid at 500 mg twice a day for 5 days [58], and tranexamic acid at 250 mg four times per day for 5 days [59]) may be efficacious in improving acutely irregular bleeding [53•]. Doxycycline, a matrix metalloproteinase inhibitor, has been theorized to be effective in limiting abnormal bleeding in progestin-only contraceptive users based on action at the level of the endometrium; however, evidence does not support its use [60].

After two years of use, bleeding profiles of DMPA versus NET-EN users differed only in higher rates of amenorrhea among DMPA users [4]. CICs were developed in part to reduce bleeding irregularities commonly associated with progestin-only methods. Comparisons between POIs and CICs demonstrate increased frequency of regular bleeding patterns among users of combined hormonal injectables; however, discontinuation rates among CICs users are overall higher, mainly due to the increased frequency of injections [61].

Return to Fertility

Return to ovulation occurs from 15-49 weeks after a single DMPA injection; median time to desired pregnancy after discontinuing DMPA ranges from 24-30 weeks [62]. No significant difference in time to ovulation was found between DMPA-IM and DMPA-SC in a group of 39 women after a single injection [63]. Women with future pregnancy intentions should be counseled regarding the highly variable and unpredictable return to ovulation after DMPA use. On the other hand, NET-EN users demonstrate more rapid return to ovulation after method discontinuation [62]. CIC users have been demonstrated to have pregnancy rates after 60 days from the last injection that are no different from a comparable population without contraception [64].

Breastfeeding

Administration of hormonal contraceptive agents in the immediate postpartum period is of theoretical concern due to the biologically plausible negative effect on breast milk production which is thought to occur in conjunction with a physiologic decline in hormones after delivery [65]. However, there are no conclusive data regarding outcomes on milk quantity and quality and breastfeeding duration among hormonal contraceptive users due to lack of high quality analyses [13••, 66]. Current US MEC guidelines do not limit DMPA administration in the postpartum period for appropriate candidates regardless of breastfeeding status [13••]. However, the WHO MEC cautions administration of POIs at less than six weeks postpartum among breastfeeding women due to the potential effect on breastfeeding, and pre-clinical data suggesting a theoretical risk of progestin exposure to the developing neonate that leads to future learning disability [12••, 67]. The guidelines note that in a setting where contraception access is limited, the risks and benefits of POI administration should be weighed against repeat pregnancy morbidity and mortality [12••].

Similarly, WHO does not recommend CIC use at less than six weeks postpartum among breastfeeding women, and cautions against use until at least six months [12••]. Of note, this guideline is stricter than the corresponding US guidelines for CHC use in the postpartum period [13••]. This difference highlights the disparities in certain settings where access to safe potable water is not available and breastfeeding may be the only source of safe nutrition for a neonate. CIC administration is not recommended postpartum until at least 21 days among healthy women due to possible increased venous

thromboembolism risk, regardless of breastfeeding status [12••].

Bone Mineral Density

DMPA's inhibition of gonadotropins results in a relative hypoestrogenic state, leading to reversible reduction of bone mineral density (BMD), the amount of minerals such as calcium per volume of bone [68]. In November 2004 the US Food and Drug Administration (FDA) issued a black box warning in the DMPA drug labeling cautioning about the "unknown" risks of BMD loss from using the medication [69]. Since then, ongoing investigations focus on the clinical significance of transient BMD loss among DMPA users. Among women less than age 45 years, there is a lack of data correlating BMD with fracture risk. A retrospective cohort study in the UK demonstrated increased trauma-related fractures among DMPA users aged 15-65 years before and during use. There was no difference in fragility fractures compared to non-users, suggesting inherent differences among women choosing DMPA, but no increased fracture risk specifically related to DMPA use [70•].

Adolescent users of DMPA are of particular interest due to concern about BMD loss at a period in time when bone mineral accrual is typically highest. However, investigations including both adolescents and adults with follow-up after five years of DMPA discontinuation have reported significant or complete reversal of bone density loss; recovery at the hip and femoral neck was more rapid than at the lumbar spine [68]. More research is needed to determine if adolescent use of DMPA is detrimental to bone health in adulthood.

Studies comparing users versus non-users of DMPA at the time of menopause suggest rapid BMD loss in non-users and attenuated loss in current users, suggesting that bone loss due to lack of estrogen from DMPA is not compounded by menopause [71]. Overall, the loss of BMD associated with DMPA and associated recovery is similar to the reversible losses during pregnancy and breastfeeding [72]. A randomized trial of 116 DMPA-SC and 109 DMPA-IM users reported no significant difference in BMD loss between the two formulations at the hip and lumbar spine with two years of continuous use [3].

DMPA is a safe and efficacious contraceptive method suitable for many women including those who are not candidates for estrogen, and there is a dearth of high quality data to suggest DMPA increases risk of fracture or bone health morbidity [73]. As such, professional organizations support the use of DMPA for contraception among appropriately counseled women [74]. Correspondingly, US MEC designates DMPA as Category 1 (no limitations on use) for healthy women aged 18-45 years, and Category 2 (benefits typically outweigh risks) outside this age range due to limited data regarding risks of BMD loss in adolescence and menopause [13••]. The American College of Obstetricians and Gynecologists recommends against routine BMD screening for DMPA users, but use of appropriate clinical judgment among women who may be otherwise at risk for poor bone health (chronic steroid use, chronic renal disease, etc.) [68]. Exercise, smoking cessation, and Vitamin D and calcium supplementation should be recommended to all patients as indicated for bone health [68]. Estrogen supplementation for the purpose of mitigating BMD loss is not recommended in adolescent or adult DMPA users [68]. Similarly, bisphosphonates or selective estrogen receptor agonists are not routinely recommended [71].

Weight Gain and Obesity

Limited evidence suggests modest weight gain in DMPA users only in comparison to non-hormonal contraceptive users. A recent study of 427 DMPA, etonogestrel (ENG) implant, levonorgestrel intrauterine device (LNG IUD), and copper IUD users reported that DMPA and ENG implant users had significantly increased mean weight gain of 2.04 and 1.96 kg, respectively, at 12 months in comparison to copper IUD users; however, the association did not persist after controlling for race and age [75•]. A retrospective study of DMPA, CHC, and CIC users for up to 12 months found similar modest weight gain with each agent [76]. No difference in weight gain was noted in DMPA-SC versus DMPA-IM users followed up to three years [77]. Women with a weight increase of greater than 5 % from baseline in the first six months of DMPA use may be at risk of continued excessive weight gain with ongoing use [78]. A review demonstrating that obese adolescent DMPA users may be at risk for excessive weight gain [79] led to a Category 2 designation for obese women less than 18 years of age [12••, 13••].

Clinical studies suggest DMPA users may undergo increases in total body fat percentage [80, 81] and fasting serum glucose and insulin levels [82]; this phenomenon may be exacerbated in obese women [83]. Additional studies are warranted to further investigate these findings and their clinical implications. Injectable contraceptive agents are generally believed to be efficacious for women regardless of BMI [84]. DMPA and NET-EN are MEC Category 1 for obese adults with BMI≥30 kg/m^2 [12••, 13••].

CICs are designated category 2 for women with a BMI≥ 30 kg/m^2 due to presumed increased risk of VTE, though absolute risk remains low [12••]. Additionally, CICs have not been demonstrated to cause clinically relevant cardiometabolic changes [64].

HIV Acquisition, Progression, and Transmission

In recent years numerous observational studies have reported conflicting evidence concerning amplified risk of human

immunodeficiency virus (HIV) acquisition among POI users. Some studies have shown a 1.5-2.2 times increased risk of HIV acquisition among DMPA users while others have shown no effect; no study has shown increased risk with NET-EN use [85]. Data interpretation is limited by heterogeneity and potential bias [85]. In July 2014, WHO issued a guidance reiterating its 2012 recommendation that no restrictions be placed on the use of injectable contraceptives, including in areas with high HIV prevalence [86•]. If further research confirms an association between HIV acquisition and DMPA, recommendations for limiting DMPA use should be region-specific, based on risks of undesired pregnancy and maternal morbidity and HIV prevalence [87]. Multiple analyses of DMPA pharmacokinetics among concomitant users of highly active antiretroviral therapy do not demonstrate efficacy or safety concerns [88]. There is no evidence suggestive of HIV progression with use of progestin-only contraceptives [86]. WHO and US MEC continue to list DMPA, NET-EN, and other hormonal methods at Category 1 for women infected with HIV [12••, 13••].

Mood Changes

There are minimal data regarding the risk of change in mood with use of DMPA, but the majority of available evidence shows no link between depressive disorder and progestin-only contraceptive use [89–91]. One case-control study showed an increased risk of depression among DMPA users versus non-users; however, the group who initiated DMPA had a significantly higher baseline rate of depression [92]. Evidence does not suggest that immediate postpartum administration of DMPA increases risk of postpartum depression [93]. Both WHO and US MEC rate DMPA as a category 1 contraceptive agent for women with depression [12••, 13••]. A recent study demonstrated a decrease in serotonin receptors in rat brains after DMPA injection when followed up to 50 days, which suggests a possible model for why mood changes could occur [94]. Unfortunately, no studies have evaluated the safety of DMPA in women with ongoing depressive disorder, bipolar disorder, or history of postpartum depression. New onset depression is rare with CIC use and is cited as a reason for discontinuation less than 1 % of the time [64].

Conclusion

Injectable contraceptive agents fill an essential family planning niche, and will continue to gain relevancy as protocols are established for home administration and distribution by community-based health workers. Women who have significant comorbidities precluding the use of estrogen are ideal candidates for DMPA or NET-EN, especially women with other co-existing conditions including sickle cell anemia, seizure disorder, endometriosis, or fibroids. DMPA use is known to decrease the risk of endometrial cancer, and is not associated with the development of other gynecologic malignancies. Injectable contraceptive agents are effective for obese women, but more research is needed to understand the clinical significance of cardio-metabolic disturbances. All progestin-only contraceptive methods cause bleeding disturbances, and women should be counseled regarding this side effect and the fact that treatment is available for acute heavy bleeding. Recommendations for use of DMPA postpartum depend on the clinical setting and breastfeeding goals. DMPA is associated with reversible bone loss but not increased risk of fracture in premenopausal women. No high quality evidence demonstrates an increased risk of HIV acquisition, but research is continuing. Future research aims include development of lower doses or alternative progestin formulations to enhance longevity of POIs and diminish side effects.

CICs are not as widely distributed but are highly effective injectable agents with fewer bleeding abnormalities and offer an excellent contraception choice for women agreeable to monthly injection. More research is needed to determine whether injectable estrogen is safe for women who have traditionally not been candidates for combined hormonal contraception.

Compliance with Ethics Guidelines

Conflict of Interest Kristen Wolfe declares that she has no conflict of interest.

Catherine Cansino reports that she is part of the speaker's bureau for Merck.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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